REMARKS

This is a response to the final office action dated June 12 of 2008. Claims 1-99 were presented originally at filing. As a result of a restriction requirement, the claims 3, 8-11, 17-18, 20-22, 24-91 and 93-99 were withdrawn. Hence, claims 1-2, 4-7, 12-16, 19, 23 and 92 remained pending.

Within this response, claims 1 and 13 are amended and claim 100 is newly added. Claims 1 and 13 are amended to recite "optical coherence tomography", also known by the acronym "OCT". Accordingly, specification paragraphs 12, 17, 32, 42, 44, 45, 47 and 65 are amended to correct a typographical error associated with the expansion of the acronym OCT. Within these specification paragraphs "optical coherence tomography" (OCT) is replaced for "optical coherence topography". Support for these amendments can be found in specification paragraph 86, which recites, "A significant reduction in nerve fiber thickness in AD subjects compared to normal subjects has been observed using OCT Humphreys". The terminology "OCT Humphreys" refers to a type of OCT that is described in an article titled " Repeatability and Reproducibility of Macular Thickness Measurements with the Humphrey OCT System", which is provided herein by the Applicant. No new subject matter has been added to the subject patent application.

Within the most recent final office action of June 12, 2008, the Examiner has rejected all of the pending claims 1-2, 4-7, 12-16, 19, 23 and 92 as being unpatentable over a patent reference to Hohla (7,237,898) in view of a patent reference to Febbroriello (7,166,079).

As now currently amended, independent claim 1 recites in part,

"... at least one imager configured to provide image data comprising at least two data types selected from the group consisting of data from ophthalmic images using confocal microscopy data, retinal polarimetry data, optical coherence tom[p]ography data, thermal image data, spectroscopic image data, refractometry data, and visible image data ...".

As now currently amended, claim 13 recites in part,

"superimposed data obtained from at least two images comprises data obtained from at least two different data types selected from the group consisting of data from ophthalmic images using confocal microscopy data, retinal polarimetry data, optical coherence tom[p]ography data, thermal image data, spectroscopic image data, refractometry data, and visible image data".

The Hohla reference employs "data 112 from corneal surface topography system 100", which is unlike data from optical coherence tomography (OCT) as now recited within the language of claims 1 and 13. Topography data describes a surface of a body. Tomography data describes what is below the surface of a body, such as a cross section of a body.

Furthermore, Hohla does not employ two different data types now recited within claims 1 and 13. For example, Hohla does not appear to employ data types including such as confocal microscopy data, retinal polarimetry data, thermal image data and spectroscopic image data as are employed within the Applicant's invention. As indicated by the Examiner, Hohla describes data associated with "topography 118" and an "iris image 120" (Column 21, Lines 54-55), and further describes "wavefront sensor data 130" and "iris image data 132" (Column 22, Lines 15-19) . Of the types of data listed within the Applicant's claim 1, the above listed types of data described within Hohla, appear to fall, at most, within the scope of one single ophthalmic data imaging type, namely "visible image data".

As stated by the Examiner, Hohla does not specifically disclose a result "that is indicative of a presence of an abnormality that appears to involve a retinal portion of the eye, and where said abnormality could actually involve, at least in part, a diseased portion of the brain" as also recited within the Applicant's claim 1. The Applicant agrees with this statement.

With respect to the Febbroriello reference, the Examiner states that "Febbroriello discloses results that is indicative of a presence of an abnormality that appears to involve a retinal portion of the eye, and where said abnormality could actually involve, at least in part, a

diseased portion of the brain (col. 3, lines 46-54)". The Applicant respectfully disagrees with this statement.

Within the cited text (col. 3, lines 46-54), Febbroriello states in part "for retinal abnormalities to be diagnosed ... correctional abilities of the body can be brought into play ... the early stages of AMD or macular hole formation, this minor loss might be visualized if conditions could be found to take advantage of the timing of retinal/brain signal processing so as to bypass the brain's compensation and corrective stages of image processing".

Febbroriello does not describe "a diseased portion of the brain" that appears to involve (affect) a "retinal portion of the eye" as recited by the Applicants claim 1. Instead, what Febbroriello describes is a diagnosis of a retinal abnormality that employs bypassing the brain's compensation and corrective stages of image processing". Furthermore, Febbroriello does not employ an "ophthalmic image" as described within the Applicant's claim 1. Instead, Febbroriello relies on the patient (user) to observe a visual abnormality and to describe that visual abnormality to a health care professional (Column 8, Lines 1-2 and 20-21).

Hence, the Applicant's goal is to identify a brain abnormality via observations of a retinal portion of the eye. Febbroriello's goal is to identify a retinal abnormality, not via observations of an abnormal brain, but instead via circumvention of some of the functions of a normal brain and observation of a visual abnormality. Although the subject matter of the Applicant's invention and Febbroriello relate to the retina and the brain, the description of the subject matter within the Applicant's specification and Febbroriello are entirely different from each other.

Consequently, no hypothetical combination of Hohla and Febbroriello could constitute subject matter that would fall within the scope of the Applicants claim 1. Furthermore, because the subject matter of Hohla is directed towards the front portion of the eye (cornea), and the subject matter of Febbroriello is directed towards the rear portion (retina) of the eye, there appears to be no motivation for one skilled in the art to combine Hohla with Febbroriello for any particular purpose.

Pending claims 2, 4-7, 12-16, 19, 23 and 92 also stand rejected as being unpatentable over Hohla (7,237,898) in view of Febbroriello (7,166,079).

As a matter of law, because independent claim 1 distinguishes over the cited art of record, namely Hohla (7,237,898) in view of Febbroriello (7,166,079) as explained above, claims 2, 4-7, 12-16, 19, 23, 92 and newly added claim 100, which depend from claim 1, also distinguish over the cited art applied by the Examiner.

In summary, based upon the above remarks and claim amendments, the Applicant asserts that the pending claims 1-2, 4-7, 12-16, 19, 23, 92 and 100 of the subject patent application are in condition for allowance and patentable over the cited art applied by the Examiner. Applicant respectfully requests a prompt notice of allowance.

If the Examiner wishes to expedite disposition of the subject patent application, he is invited to contact Applicant's representative at the telephone number listed below.

It is believed no fee is required for the filing of this response. However, in the event that any additional fees are required, the Director is hereby authorized to charge Deposit Account No. 50-3010 for any additional fees and to charge any overpayments thereto.

Respectfully submitted,

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Repeatability and Reproducibility of Macular Thickness Measurements with the Humphrey OCT System

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Purpose. To assess the accuracy, precision, repeatability, and reproducibility of measurements made by the Humphrey optical coherence tomography (OCT) system (Humphrey-Zeiss Medical Systems, San Leandro, CA).

Methods. The performance of the system was first investigated by scanning a test object containing an air gap of known size. Measurements were repeated with water or glycerin in the gap. In the clinical setting, macular thickness measurements were obtained from a control group of 20 normal subjects. For analysis, these scans were divided into eight sections, each containing 10 A-scans.

Results. The average gap thickness was found to be close to the true value in all cases. The overall coefficients of intersession reproducibility were less than 1% for the test object and 1.51% for the control group. There was no significant difference between scans acquired during different sessions. The overall coefficients of repeatability for the test object were between 0.2% and 1.1% and between 1% and 2% for the control group. The range of normal retinal thickness in terms of the 5th and 95th percentiles was 222 to 248 μm in women and 234 to 257 μm in men.

Conclusions. Measurements made from OCT scans were found to be accurate and precise. Introducing water or glycerin into the test object resulted in considerable degradation of the signal, but measurements of gap thickness were still shown to be accurate, precise, reproducible, and repeatable. Retinal thickness measurements in the macular area were repeatable and reproducible. This demonstrates that OCT is a useful tool in the monitoring of patients with conditions that affect macular thickness, even when there is considerable degradation of the OCT signal. (*Invest Ophthalmol Vis Sci.* 2002;43:490–495)

Optical coherence tomography (OCT) is becoming an increasingly popular imaging tool in ophthalmology because of its ability to yield cross-sectional images of the retina with a resolution that is considerably greater than that obtained from ophthalmic ultrasound. A number of publications have provided detailed descriptions of the functional characteristics of OCT[1–3] and of the application of this technique in the clinical environment.[3–13] The OCT software is designed to make measurements of retinal thickness or nerve fiber layer (NFL) thickness from the acquired scans, a feature that permits more effective monitoring of patients with conditions that cause variations in retinal or NFL thickness, such as diabetes, glaucoma, and diseases that lead to macular edema. There have been several publications that demonstrate the value of this measurement facility in the clinical setting.[14–25]

To evaluate changes in macular thickness it is first necessary to determine the range of retinal thickness in the normal population and to quantify the accuracy, reproducibility and repeatability of measurements made by the system. At present, there is only one commercially available OCT system, manufactured by Humphrey-Zeiss Medical Systems (San Leandro, CA), and several groups have evaluated the repeatability or reproducibility of both this prototype system and the commercially available one and have published values for the range of retinal thickness or NFL thickness in a control population.[14,16,26–31] However, there do not seem to be consistent definitions of the terms repeatability and reproducibility. One purpose of this study was therefore to quantify both the repeatability and the reproducibility of the commercially available OCT scanner by basing our definitions of repeatability and reproducibility on the standards set by the British Standards Institution and the International Standards Organization,[32,33] as recommended by Bland and Altman.[34] In addition to assessing repeatability and reproducibility, it is important to quantify the accuracy and precision of the measurements made by the system, a concern that does not appear to have been investigated so far. It is also worth assessing the performance of the equipment in situations in which the reflected OCT signal is somewhat degraded and boundaries are less well defined. Thus, another purpose of this study was to analyze the performance of the system by scanning a custom-built object of precisely known size under three different conditions.

Materials and Methods

Equipment

The scanner used in this study was the commercially available OCT scanner manufactured by Humphrey-Zeiss Medical Systems. Scanning is performed using a superluminescent diode operating with a wavelength of 850 nm and maximum power of 750 μW. Each B-scan consists of 100 A-scans, regardless of the length of the scan line, and images are displayed as a pseudocolor plot in which different colors represent differences in the reflective properties of the retinal tissue.

The custom-built test object consisted of two 1-cm-thick plates of glass separated by four 200-μm-thick spacers. The thickness of the spacers was known to an accuracy of 0.5 μm. A technique called optical contacting made it possible to attach the spacers to the glass plates without the use of any sort of adhesive. This technique is a process by which two surfaces adhere to one another through molecular attraction. The surfaces of the plates to be contacted are parallel to within 0.5 arc-second, extremely flat, and cleaned to an exceptionally high degree. When brought together, the surfaces then adhere with no adhesive. This technique ensures that the thickness of the gap corresponds exactly to the thickness of the spacers. Thus, this object basically provided us with a gap of precisely known thickness. This gap could also be filled with liquids. Scans of the test object resulted in two reflecting bands representing the glass–air or glass–liquid boundaries. The plates of the test object were made of fused silica with a refractive index of 1.452 at 840 nm. Thus, imaging of the air-filled gap resulted in very strong reflections due to the large change in refractive index at

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the boundary. In the eye, reflections tend to be less pronounced; and to model the in vivo situation more effectively the experiment was therefore repeated with the gap filled with water (refractive index, 1.333) and glycerin (refractive index, 1.473). This had the effect of degrading the intensity of the reflected signal and making the glass–liquid boundary far less well defined.

The OCT software assumes a refractive index of 1.38 for retinal tissue (this index value was provided by the manufacturers of the system); thus, measurements made from the A-scan were multiplied by this index to convert them back into measurements in air. These values were then divided by the refractive index of the material within the gap to arrive at the true gap thickness, as measured from the OCT scan. The results were then compared with the known thickness of the gap.

Subjects

Twenty volunteers (10 men and 10 women), ranging in age from 21 to 57 years (average age, 31.9 years) participated in this study. The study was conducted according to the tenets of the Declaration of Helsinki, and volunteers gave informed consent after the nature and intent of the study had been fully explained to them. The exclusion criterion was history of known retinal disease. All scanning was performed in the right eye, which was dilated with 1% tropicamide.

Scanning

The known distance between the plates of the test object assumes an incident beam normal to the sample. Thus tilting the sample would increase the distance traveled by the OCT beam, leading to a higher measurement. Each pixel within the A-scan represents a distance of 4 μm in retinal tissue that corresponds to 5.5 μm in air, 4.1 μm in water and 3.7 μm in glycerin; thus, OCT measurements can distinguish only between measurements that vary by more than these amounts. From geometric calculations and experimentation, it was found that tilts within 10° from normal caused inaccuracies that were less than the intrinsic thickness resolution of the system. Thus, the positioning of the test object was not particularly critical for making accurate measurements. It was observed that the intensity of the reflections from the interfaces varied with different focusing and polarization settings. In the case of the air-filled gap, these were adjusted to give the strongest possible signal. Several scans across the surface of the object were then acquired.

For the cases in which the gap was filled with liquid, we wanted to quantify the degradation of the signal. The object was first set up with an air-filled gap, as just explained, and then the liquid was introduced carefully without altering the position of the object or the polarization and focusing settings. Scans were acquired before and after the liquid was inserted, so that the reduction in intensity of the reflections could be assessed.

In our study of normal subjects we initially took a series of horizontal single-line scans across the fovea in each subject. Scans were repositioned, using the repeat-scan feature that provides a landmark cursor to facilitate the repeat positioning of subsequent scans. We then discarded any scans in which the landmark cursor was not in the correct position, thus ensuring that all the saved scans were of exactly the same portion of retina. However, after careful analysis of the fundus pictures it was discovered that there was a degree of inaccuracy in the positioning of this landmark cursor. We found that there was some displacement, even between scans in which the landmark cursor appeared to be in exactly the same position. This displacement was of the order of 0.2 to 0.3 mm. In the region of the fovea where the thickness of the retina is varying, a shift of this amount could cause considerable variations in the measured retinal thickness and would lead to inaccuracies in the coefficients of repeatability and reproducibility.

In an attempt to minimize the effects of landmark positioning errors, we therefore decided to scan across a band rather than across a single line. This was achieved by having a number of very closely spaced scan lines using the raster six-lines option, which allows six tomographic scans to be acquired in succession. In this scanning mode, an aiming rectangle of adjustable dimensions is displayed on the fundus-viewing unit. The width of this rectangle determines the length of the scan lines, whereas its height determines the spacing between the scans. In this case, the width of the aiming rectangle was set at 4 mm and its height was 0.5 mm. Thus, the spacing between successive scans was 0.1 mm. The aiming rectangle was positioned such that at least four of the scans traversed and were centered on the foveal pit. These four scans therefore covered a vertical length of 0.3 mm, which corresponds to the maximum error in positioning found from our initial investigation. These four scans from each group were then used in subsequent calculations. The focusing and polarization settings were adjusted so that the best-quality image was obtained.

Our definitions of repeatability and reproducibility were based on the definitions adopted by the British Standards Institution.[32,33] Under repeatability conditions, independent test results are obtained with the same method on the same subject by the same operator and on the same set of equipment, with the shortest time lapse possible between successive sets of readings. We investigated repeatability initially on the test object by acquiring 10 scans in rapid succession. Repeatability on the control group was investigated by obtaining 10 sets of six tomographic scans from the same subject. All scanning was performed by the same operator. The time elapsed between successive sets of scans corresponded to the time taken to set up and position the aiming rectangle for a new set of tomographic scans and was always less than 1 minute. Repeatability was investigated for three different subjects.

Under reproducibility conditions sets of readings are obtained using the same method but on different occasions. Intersession reproducibility for the test object was investigated by acquiring readings in the morning and afternoon on five consecutive days. The time separation between the morning and afternoon sessions was at least 5 hours, and the OCT scanner was not switched off during this period. The temperature of the room varied by approximately 2° during that time. We then analyzed intersession reproducibility in the clinical setting for each of the 20 subjects by obtaining two sets of six tomographic scans with a minimum time separation of 30 minutes.

Analysis

A-scans of the test object showed two peaks corresponding to the edges of the air gap. We decided to measure the thickness of the gap by considering the distance between the two maxima. Computer programs that identified the peaks and calculated the distance between them were developed, because the software provided with the OCT scanner could not perform these functions. When the gap was filled with air, the gap edges were very well defined, and the two maxima corresponding to the glass–air interfaces were easily identifiable on each of the A-scans. Filling the gap with either water or glycerin caused a reduction in the overall intensity of the reflections from the interfaces. At some positions along the scan line, the returning reflection was so weak that it fell below the noise threshold, and this meant that the gap edges no longer appeared as continuous lines on the B-scan but had a more patchy appearance. At these positions, it was impossible to identify the two maxima corresponding to the gap edges from the A-scan. Thus, thickness measurements were made only from the A-scans in which the two maxima could clearly be identified.

To quantify the degradation of the signal caused by introducing a liquid into the air gap we calculated the percentage reduction in reflectance. For each B-scan acquired as part of the repeatability study, we selected the A-scans in which the two maxima were clearly identifiable and quantified the intensity of the reflections from the interfaces These values were then averaged over the entire B-scan. This value was then divided by the average intensity calculated from the scans acquired just before the liquid was introduced. In the water-filled condition, the intensity of the reflection from anterior edge of the gap (closest to the machine head) was found to be 48.5% of the air-filled condition; for the posterior edge it was 57.0%. With glycerin in the gap, these values were 42.9% for the anterior edge and 47.7% for the posterior.

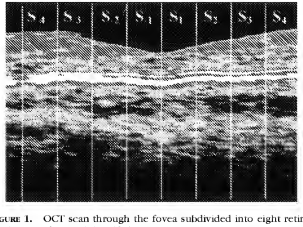

FIGURE 1. OCT scan through the fovea subdivided into eight retinal sections, each containing 10 A-scans.

For the water-filled gap, an average of 97 A-scans per B-scan showed two easily identifiable maxima, whereas in the glycerin-filled condition this value was 45 A-scans per B-scan.

In the normal control study, four scans that traversed the foveal pit were selected from each set of six tomographic scans, and only these were used for determining the coefficients of repeatability and reproducibility. These scans were labeled level 1 to level 4, with level 1 being the most inferior scan of the set. The retinal thickness along each point of each scan was found by using the retinal thickness tool provided with the OCT software. This software assumes that the first highly reflecting band corresponds to vitreoretinal interface and that the second corresponds to the retinal pigment epithelium. Thus, retinal thickness measurements are made by evaluating the displacement between the anterior surfaces of these two interfaces. The results from this tool cannot be exported directly from the system; however, the manufacturer provides a separate program that exports this data as a text file. Thickness values were thus exported for each scan, and any obvious errors in boundary detection were corrected manually.

The center of each scan was taken to be the thinnest point of the retina, which was assumed to correspond to the deepest portion of the foveal pit. The A-scan at the center of the scan was labeled A_0. Scans to the left of this were labeled A_{-1} to A_{-49}, and scans to the right were labeled A_1 to A_{50}. Each scan was then divided into eight sections, each containing 10 A-scans. Sections to the left of the center were labeled S_{-1} to S_{-4} and those to the right were labeled S_1 to S_4 as shown in Figure 1. Thus, for each B-scan, only the 80 A-scans from A_{-39} to A_{40} were used in the calculations. The retinal thickness obtained from each of these 80 scans was averaged across the four levels in each set in an attempt to minimize the effects of errors in scan positioning. Thus, we were left with a single set of 80 thickness values from each group of tomographic scans. The overall average retinal thickness (the average of these 80 thickness values) and the average retinal thickness per section were calculated for each group of data.

The median and the 5th and 95th percentiles of the overall retinal thickness and retinal thickness per section were calculated for the sample as a whole, as well as for the women and men alone, because Hee et al.[14] found that the foveal thickness is significantly different between men and women. This group used the Student's *t*-test for their analysis, which implies that the data are normally distributed. However, we opted for nonparametric tests, because we could not be sure that the retinal thickness in the macular region follows a normal distribution.

As suggested by Bland and Altman[3,4] who based their definitions on the recommendations of the British Standards Institution, the coefficient of intersession reproducibility was defined as the SD of the differences between pairs of measurements obtained during different sessions divided by the average of the means of each pair of readings. Intersession repeatability was evaluated for the test object from the average air gap thickness computed from each session. The overall coefficient of intersession reproducibility for the control group was calculated from the 20 overall average retinal thickness values. Coefficients of reproducibility were also calculated for each of the eight retinal sections. A graph of differences against means was plotted both for the overall average retinal thickness and for each section. In both cases, the Wilcoxon matched-pairs test (5% significance level) was also used to establish whether there was any statistically significant difference between measurements obtained during different sessions.

The coefficient of repeatability obtained from the repeated administration of the test under identical conditions was defined as the SD of the difference from the mean of these repeat measurements divided by the average response. Coefficients of repeatability were calculated from the 10 consecutive scans of the test object, as well as in each of the three subjects participating in the repeatability study.

To establish whether scanning across a 0.3-mm band of retina, rather than across a single line, actually improved the repeatability, we also computed the coefficient of repeatability for each level and compared that with the value obtained from the average over four levels.

RESULTS

Gap Thickness Measured from Test Object

The average gap thickness was calculated from the individual A-scan thicknesses for each of the 10 consecutive scans in the repeatability study in all three subjects. These values were then averaged over the 10 scans, and the final values for average gap thickness were found to be 197.7 ± 0.6 (air-filled), 195.1 ± 0.7 (water-filled), and 196.1 ± 1.7 μm (glycerin-filled).

Intersession Reproducibility

Test Object. The average gap thickness was calculated from the individual A-scan thicknesses for each morning and afternoon session. These values were then used to compute the overall coefficients of intersession reproducibility, which were found to be 0.67% (air-filled), 1.05% (water-filled), and 0.45% (glycerin-filled). The Wilcoxon paired-measurement test (5% significance level) showed that there were no statistically significant differences between the measurements obtained in the morning and afternoon scanning sessions.

Control Group. For each subject the overall average retinal thickness was calculated for sessions 1 and 2. The overall coefficient of reproducibility was then computed from these values and was found to be 1.51%. In addition, we found the average retinal thickness for each of the eight sections and computed the coefficient of intersession reproducibility for each section. The results obtained are shown in Table 1. The intraclass correlation coefficient (ICC) for intersession reproducibility was found to be 0.96. Graphs of differences against means were plotted for the overall average retinal thickness values, as well as for each section. We have shown only the graph of differences against means for the overall retinal thickness (Fig. 2); the graphs for the individual sections were very

TABLE 1. Coefficient of Reproducibility, Overall and for Each Retinal Section

	Coefficient of Reproducibility (%)
Overall	1.51
S_{-4}	1.99
S_{-3}	2.24
S_{-2}	3.49
S_{-1}	4.20
S_1	4.04
S_2	2.98
S_3	1.24
S_4	1.62

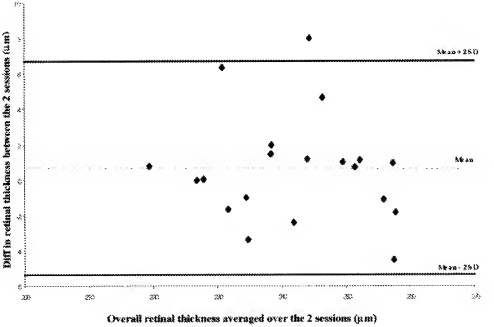

FIGURE 2. Graph of data from inter-session reproducibility study. Mean retinal thickness for each subject is plotted against difference in retinal thickness between morning and afternoon scanning sessions. Ninety-five percent of the values (19 of 20) fell within 2 SDs of the mean.

similar in appearance. In all cases it was found that 95% (19 of 20) of differences fell within 2 SDs of the mean. According to the definitions of the British Standards Institution[33] this indicates reproducibility in overall and sectional retinal thickness measurements. The Wilcoxon paired measurement retest (5% significance level) was also performed on the overall retinal thickness values and on the values for each retinal section. No statistically significant differences were found between the two sets of data. There is therefore no evidence to suggest that slight variations in room temperature (on the order of 2°C) have any effect on the performance of the OCT scanner. With a study involving 20 patients, the probability is 80% that the study will detect a difference in morning and afternoon sessions if the true difference between sessions is 2.18 μm (two-tailed 5% significance level).

Repeatability

Test Object. The coefficients of repeatability, calculated from the average gap thickness computed for each of the 10 consecutive scans, were found to be 0.29% (air-filled), 0.34% (water-filled), and 0.43% (glycerin-filled).

Control Group. For each of the three subjects in the repeatability study we computed the overall coefficient of repeatability by analyzing the overall average retinal thickness from each set of readings. We then computed the coefficient of repeatability for each of the eight retinal sections. The results obtained are shown in Table 2.

To determine whether averaging over four levels had any significant effect on the repeatability of the measurements, we also computed the overall and per-section single-level coefficient of repeatability for each of the four individual levels. We then averaged these values for each section and compared the results with the values obtained for the multiple-level case. The results for the single-level coefficients of repeatability are shown in Table 2.

Retinal Thickness

The median and the 5th and 95th percentiles of the overall and sectional retinal thickness values are shown in Table 3.

For comparison with the results of Koozekanani et al.,[27] we calculated the average retinal thickness for sections S_3 and S_4 together, which was found to be 271 ± 16 μm. We also calculated the average retinal thickness for sections S_1 and S_{-1} and found that this was 178 ± 18 μm in the women and 190 ± 24 μm in the men. Wilcoxon analysis (5% significance level) showed that there were statistically significant differences in the overall average retinal thickness in the men and women (values were higher for the male subjects in the study).

DISCUSSION

Before using measurements made from OCT scans as part of a clinical diagnosis of a condition, it is necessary to ensure that the repeated scans give consistent results. Our study on the air gap in the test object showed a high degree of repeatability (0.29%). Even with considerable degradation of the OCT signal and poorly defined interfaces, the coefficients of repeatability were still under 1%. The measurements made from the control group showed that the overall coefficients of repeatability were between 1% and 2% and sectional coefficients of repeatability were all less than 5%. As expected, these values were slightly lower than for the test object, due to the introduction of additional errors, such as inaccuracies in positioning of

TABLE 2. Coefficients of Repeatability, Overall and for Each Retinal Section and for the Multiple-Level and Single-Level Case

	Subject 1		Subject 2		Subject 3	
	ML	SL	ML	SL	ML	SL
Overall	1.07	1.62	1.27	1.75	1.98	2.88
S_{-4}	1.93	2.36	0.75	1.36	1.58	2.41
S_{-3}	1.28	1.87	1.08	1.74	1.58	2.39
S_{-2}	1.70	3.07	3.19	4.30	2.15	3.18
S_{-1}	3.56	5.69	4.03	5.60	4.14	7.01
S_1	2.49	3.85	3.92	5.73	4.78	7.44
S_2	1.24	2.16	4.35	5.26	1.87	3.13
S_3	0.92	1.59	1.68	2.37	1.54	2.68
S_4	1.07	1.85	1.06	1.56	1.55	2.89

Data are expressed as percentages. ML, multiple level; SL, single level.

TABLE 3. Median, 5th, and 95th Percentile Values for Retinal Thickness

	Whole Sample			Females			Males		
	Median	5th	95th	Median	5th	95th	Median	5th	95th
Overall	238	225	257	233	222	248	248	234	257
S_{-4}	263	240	297	257	240	280	278	262	307
S_{-3}	263	244	292	259	243	278	280	259	295
S_{-2}	232	213	266	229	215	252	243	218	268
S_{-1}	178	154	213	174	152	202	184	160	215
S_1	187	161	218	177	160	205	197	163	222
S_2	245	221	267	239	220	251	252	229	269
S_3	273	251	289	272	247	288	276	262	289
S_4	272	242	291	272	240	286	283	249	292

scans, but nevertheless show a high degree of repeatability in the clinical setting. This indicates that within the same scanning session, measurements made by the system are repeatable, and hence for clinical applications, there is no need to take a large quantity of readings for reliable measures of retinal thickness. Our results from the liquid-filled test object indicate that even in cases in which retinal disease causes degradation of the OCT signal, provided that the position of vitreoretinal interface and the retinal pigment epithelium can be identified at a least a few positions along the scan line, measurements of retinal thickness should still show a high degree of repeatability.

The overall coefficients of intersession reproducibility were found to be between 0.67% and 1.05% for the test object and 1.5% for the control group. Sectional coefficients of reproducibility were all less than 5%. This indicates that any significant variation in retinal thickness measurements from different scanning sessions is likely to be due to changes in the patient's retinal thickness rather than to inconsistencies in the values given by the OCT system. Thus, OCT may be used to monitor patients with conditions that affect the thickness of the retina in the macular region, even in situations in which the retinal interfaces are poorly defined.

The average test object gap thicknesses computed under the three different conditions agree very closely with the known thickness of the air gap, which was 200 μm. This indicates a high level of accuracy and precision in the measurements made by the system, even in situations in which the OCT signal is relatively weak.

From Table 2 it is clear to see that the repeatability of the retinal measurements made over a band of 0.3 mm is consistently better than when repeated scans are made across a single line. This confirms that slight errors in scan positioning occur and consequently, that our method of acquiring a series of scans across a 0.3-mm band yields more reliable measures of repeatability and reproducibility of the system than simply scanning repeatedly across a single line. These errors in positioning may be partly because the quality of the fundus picture displayed on the fundus-viewing monitor is somewhat poor. Moreover, whereas in the slow-scanning mode, the landmark cursor tends to lose its definition, thus making it very difficult to ensure that it remains in the correct position. It is hoped that future versions of the hardware will include a better quality fundus-viewing unit that would enable more precise repeat scanning.

Our methods of quantifying repeatability and reproducibility of retinal thickness measurements in the foveal region differ slightly from those used in other publications; however, the results obtained are quite similar. Koozekanani et al.[27] analyzed sets of scans obtained during independent measuring sessions. They found that there were no significant differences between different sessions or between different scans within the same session; however, they do not specify which statistical test was used. We performed the Wilcoxon matched-pairs test on the data obtained under reproducibility conditions and found that there were no significant differences between the sets of data acquired during different scanning sessions. This is true both for the overall retinal thickness as well as for the thickness in each retinal section.

Our method of subdividing each scan into sections containing 10 A-scans is very similar to the system adopted by Baumann et al.[26] They divided their images into seven regions, each containing 10 A-scans, and computed the coefficient of variation for retinal thickness measurements made in each of these sections. They found that the greatest coefficient of variation occurred in the central section, which covered a retinal length of 320 μm centered on the foveal pit. Sections closest to the fixation point showed less reproducibility than those farther away. We calculated the coefficients of repeatability and reproducibility for each of our retinal sections and similarly found that these coefficients tended to be highest for regions S_1 and S_{-1}, which correspond to the sections closest to the center of the fovea. In this region the retinal thickness varies, and hence any errors in scan positioning will causes variations in the measured thickness of this region. We have attempted to compensate for this by scanning across a 0.3-mm band. However, although we have shown that this reduces the effects of errors in positioning, the higher coefficients of repeatability and reproducibility in these regions relative to other regions indicate that there is still a degree of inaccuracy in the positioning of scans.

It is also important to establish confidence intervals for retinal thickness in the normal population. We therefore computed the median and the 5th and 95th percentiles for retinal thickness in the macular region. Our control group was not ideal, because all our subjects were relatively young. Nevertheless, our results compare very well with those obtained by other investigators.

The size of our sample and the mean age are similar to those investigated by Baumann et al.,[26] and our sectional results are comparable to those quoted in their publication. The average retinal thickness for sections S_3 and S_4 together was 271 ± 16 μm. This represents an average over an 0.8-mm section of retina at a distance of 0.8 mm from the foveal pit, and the result is almost identical with the average retinal thickness of 274 ± 17 μm of Koozekanani et al.[27] for a 1-mm section at a distance of 0.75 mm from the foveal pit. The average retinal thickness for sections S_1 and S_{-1} together was 178 ± 18 μm in the women and 190 ± 24 μm in the men. These values are higher than the foveal thicknesses of Hee et al.[14] of 169 ± 4 μm for the female and 181 ± 4 μm for the male subjects. This difference is probably because Hee et al. analyzed a circular region of 500-μm diameter, whereas our analysis was performed on a larger rectangular region of 800 × 300 μm.

In this study we concentrated on total retinal thickness within the macular area and showed that measurements made in this area are accurate and precise and that they demonstrate a high level of repeatability and reproducibility. This implies that OCT can reliably be used to monitor patients with conditions that affect macular thickness. A simple model has shown that in patients in which interfaces are not very well defined, the measurements made nevertheless agree very closely with the known value of the distance being measured and that these measurements still show a high degree of repeatability and reproducibility. This has important implications for assessing changes in macular thickness in patients affected by conditions, such as macular edema, which may degrade the quality of the OCT image. In the assessment of conditions such as glaucoma and macular edema, it is becoming increasingly common to make use of six radial scans to create a retinal map. A possible extension of this study would be to assess the repeatability and reproducibility of the OCT scanner in this situation.

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